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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/568,669	11/08/2006	David B. Agus	67789-542	9540
50670 7590 09/08/2009 DAVIS WRIGHT TREMAINE LLP/Los Angeles 865 FIGUEROA STREET SUITE 2400 LOS ANGELES, CA 90017-2566				
EXAMINER				
RAWLINGS, STEPHEN L				
ART UNIT		PAPER NUMBER		
1643				
MAIL DATE		DELIVERY MODE		
09/08/2009		PAPER		

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/568,669

**Applicant(s)**

AGUS ET AL.

**Examiner**

Stephen L. Rawlings

**Art Unit**

1643

**Period for Reply** -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 11 May 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 10-19 and 29-33 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 10-19 and 29-33 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 16 February 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB08)
- 4) ☐ Interview Summary (PTO-413)
- 5) ☐ Paper No(s)/Mail Date 20080707/20080917
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

1. The election with traverse filed May 11, 2009, is acknowledged and has been entered.

Applicant has elected the invention of Group II, wherein said cancer is prostate cancer.

2. The amendment filed January 5, 2009, is acknowledged and has been entered. Claims 1-9 and 20-28 have been canceled. Claims 10-12 have been amended. Claims 29-33 have been added.

3. The amendment filed September 17, 2008, is acknowledged and has been entered in part since the amendment to the claims failed to comply with requirements set forth under 37 C.F.R. § 1.121.

4. Claims 10-19 and 29-33 are pending in the application and are currently subject to examination.

### ***Election/Restrictions***

5. Applicant's traversal of the propriety of the restriction requirement set forth in the Office action mailed April 15, 2009, is acknowledged.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

As evident in view of the following grounds of rejection of claim 1 under 35 U.S.C. § 102, the claim fails to link the inventions of Groups I and II by a common concept, or special technical feature, as defined by PCT Rule 13.1, because it does not define a contribution over the prior art.

Notably Applicant has argued that the reference cited in the rejection of claim 1 under § 102 is not prior art since, as Applicant has further argued, the effective filing

date of the claim should be deemed August 27, 2004, if not earlier<sup>1</sup>. In response, Hedvat et al. (of record) was published in June 2004 and is prior art under § 102(a).

Accordingly, the restriction requirement set forth in the Office action mailed January 4, 2008, is deemed proper and therefore made FINAL.

### ***Information Disclosure Statement***

6. The information disclosures filed July 7, 2008, and September 17, 2008, have been considered. An initialed copy of each is enclosed.

### ***Priority***

7. Applicant's claim under 35 U.S.C. §§ 119(e) and/or 120, 121, or 365(c) for benefit of the earlier filing dates of U.S. Provisional Application No. 60/498,849, filed August 29, 2003, and U.S. Provisional Application No. 60/568,910, filed May 7, 2004, is acknowledged.

However, as explained above, none of claims 10-19 and 29-33 properly benefit under § 119 by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure.

In addition, as noted in the preceding Office action mailed May 19, 2008, neither provisional application adequately describes the claimed invention, such that either disclosure is sufficient to provide written basis for the language of the present claims. For example, neither disclosure includes a description of treating a condition in a mammal by administering a NSAID and HER2-kinase axis inhibitor on a periodic basis; additionally, neither application describes such combination therapy as inclusive of gefitinib or trastuzumab, for example; furthermore, neither application describes administering either agent sublingually, for example; and finally, neither describes administering the agents in the specific ranges recited in any of the claims. While there are still other reasons that none of the claims properly benefits from the earlier filing

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<sup>1</sup> See pages 5 and 6 of the response filed May 11, 2009.

dates of either one of the provisional applications, it is apparent that the differences in the scope of the disclosures in this application and those earlier applications are substantial.

Notably Applicant has argued that Provisional Application Serial No. 60/498,849 describes a combination treatment that can increase sensitivity of epithelial cancer; such a disclosure however does not provide written support for the language of the instant claims.

Accordingly, the effective filing date of the claims is deemed the filing date of the instant application, namely August 27, 2004<sup>2</sup>.

#### ***Grounds of Objection and Rejection Withdrawn***

8. Unless specifically reiterated below, Applicant's amendment and/or arguments have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed May 19, 2008.

#### ***Grounds of Objection and Rejection Maintained***

##### ***Specification***

9. The objection to the specification because the use of improperly demarcated trademarks is maintained. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See M.P.E.P. § 608.01(v).

Although it appears that Applicant has made a *bona fide* effort to resolve this issue by appropriately amending the specification, an additional example of an improperly demarcated trademark appearing in the specification is noted, namely TaqMan™; see, e.g., page 23, line 4, of the specification, as filed.

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate

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<sup>2</sup> The preceding Office action erroneously indicated that the effective filing date of the claims is November 8, 2006, but this application is the National stage entry of the International application PCT/US04/28071.

symbol indicating its proprietary nature (e.g., <sup>TM</sup>, <sup>®</sup>), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at <http://www.uspto.gov/web/menu/search.html>.

***Claim Rejections – 35 U.S.C. § 112***

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. The rejection of claims 10-19, 29, and 30 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is maintained.

Beginning at page 10 of the amendment filed September 17, 2009, Applicant has traversed the propriety of maintaining this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Claims 10-19 are indefinite for the following reasons:

The claims are directed to "HER2-kinase axis inhibitors", but as explained in the written description rejection that follows, it is not evident which agents are "HER2-kinase axis inhibitors" and which are not.

There appears to be no common feature among those particularly named "HER2-kinase axis inhibitors". Many of those listed in claim 12, for example, either have no particular function (e.g., an antibody) or have substantially different and/or unrelated functions. For example, rapamycin is an immunosuppressive macrolide antibiotic, which inhibits T- and B-cell proliferation; but imatinib mesylate is 2-phenylaminopyrimidine derivative that inhibits the autophosphorylation of tyrosine kinases, such as Abl. Gelfitinib (ZD1839), on the other hand, is a selective inhibitor of epidermal growth factor receptor (EGFR); and trastuzumab is a humanized antibody that binds to the extracellular domain of HER2.

Given such disparity, the "HER2-kinase axis inhibitor" might be any substance that could be administered to a mammal in combination with a NSAID on a periodic basis, but presumably Applicant does not consider such broad subject matter to be the invention; so, rather than broad, it appears that the use of the term "HER2-kinase axis inhibitor" renders the claims indefinite.

It is submitted that rather than just broad, the claims are indefinite because there is simply no means of ascertaining the metes and bounds of the subject matter that is regarded as the invention; and consequently, it is submitted that the skilled artisan would not be reasonably apprised of the metes and bounds of the subject matter that is encompassed by the claims, so as to permit the skilled artisan to know or determine infringing subject matter and/or non-infringing subject matter.

What is the "HER-kinase axis"? What is an "axis"? Is the "axis" a biochemical pathway? How is an "axis" different from a "pathway"?

How are members of this "axis" known or identified? How are other proteins distinguished from its members?

Is a "HER-kinase axis inhibitor" a substance that inhibits the "axis", as a whole, or merely a substance that inhibits an activity of one of the constituent members of the "axis"?

Again, given the obvious differences in the structures and functions of those substances that are identified with particularity in the specification (e.g., trastuzumab and rapamycin), it is submitted that the answers to these questions cannot be gleaned from the disclosure, which fails to define these terms that are used in the claims to delineate the metes and bounds of the subject matter that is regarded as the invention.

As a consequence, the claims do not delineate the metes and bounds of the subject matter that is regarded as the invention with the requisite clarity and particularity to permit the skilled artisan to know or determine infringing subject matter, so as to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

In accordance with a recent decision by the Federal Circuit (*Halliburton Energy Services Inc. v. M-I LLC*, 85 USPQ2d 1654, 1658 (Fed. Cir. 2008)):

35 U.S.C. § 112, ¶ 2 requires that the specification of a patent "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." Because claims delineate the patentee's right to exclude, the patent statute requires that the scope of the claims be sufficiently definite to inform the public of the bounds of the protected invention, i.e., what subject matter is covered by the exclusive rights of the patent. Otherwise, competitors cannot avoid infringement, defeating the public notice function of patent claims. Athletic Alternatives, Inc. v. Prince Mfg., Inc., 73 F.3d 1573, 1581 (Fed. Cir. 1996) ("[T]he primary purpose of the requirement is 'to guard against unreasonable advantages to the patentee and disadvantages to others arising from uncertainty as to their [respective] rights.'") (quoting Gen. Elec. Co. v. Wabash Appliance Corp., 304 U.S. 364, 369, (1938)). The Supreme Court has stated that "[t]he statutory requirement of particularity and distinctness in claims is met only when [the claims] clearly distinguish what is claimed from what went before in the art and clearly circumscribe what is foreclosed from future enterprise." United Carbon Co. v. Binney & Smith Co., 317 U.S. 228, 236 (1942).

Applicant has argued that one of skill in the art would recognize agents that are "Her-kinase axis inhibitors", given only the functional limitations that are recited in the claims, but the only functional limitation of the agent that is reasonably read into the claims is the ability of the "HER-kinase inhibitor" to act in combination with a NSAID to treat a cancer; and the specification does not expressly define the term<sup>3</sup>. As explained, it is not at all evident which other properties particularly define members of this group of "Her-kinase axis inhibitors" or how one might know or recognize a substance that acts in combination with a NSAID to treat a cancer, which is used to practice the claimed invention.

Applicant has argued that the "Her-kinase axis inhibitor" inhibits the activation of the HER-kinase axis pathway; in reply, it is first noted that the "Her-kinase axis inhibitor" is not defined by the claim or the disclosure to be a substance that "inhibits the activation of the HER-kinase axis pathway". Secondly, since as explained it is not known and cannot be determined what components of a mammalian cell or body constitute the "HER-kinase axis pathway", it is not possible to know or determine if a substance is capable of inhibiting the activation of the pathway.

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<sup>3</sup> Less precisely, according to paragraph [0027] of the published application, the "HER-kinase axis inhibitors" used in connection with various embodiments of the present invention are only very vaguely described as possibly exhibiting anti-cancer properties.

In further response to Applicant's arguments, Applicant is reminded that in determining whether the claims satisfy the requirement set forth under § 112, second paragraph, M.P.E.P. § 2106 (II) states:

USPTO personnel are to give claims their broadest reasonable interpretation in light of the supporting disclosure. *In re Morris*, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997). **Limitations appearing in the specification but not recited in the claim should not be read into the claim.** *E-Pass Techs., Inc. v. 3Com Corp.*, 343 F.3d 1364, 1369, 67 USPQ2d 1947, 1950 (Fed. Cir. 2003) (claims must be interpreted "in view of the specification" **without importing limitations from the specification into the claims unnecessarily**). *In re Prater*, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550- 551 (CCPA 1969). See also *In re Zletz*, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) ("During patent examination the pending claims must be interpreted as broadly as their terms reasonably allow.... The reason is simply that during patent prosecution when claims can be amended, ambiguities should be recognized, scope and breadth of language explored, and clarification imposed.... An essential purpose of patent examination is to fashion claims that are precise, clear, correct, and unambiguous. Only in this way can uncertainties of claim scope be removed, as much as possible, during the administrative process.") (Emboldened added for emphasis).

M.P.E.P. § 2106 (II) continues:

While it is appropriate to use the specification to determine what applicant intends a term to mean, **a positive limitation from the specification cannot be read into a claim that does not itself impose that limitation.** A broad interpretation of a claim by USPTO personnel will reduce the possibility that the claim, when issued, will be interpreted more broadly than is justified or intended. An applicant can always amend a claim during prosecution to better reflect the intended scope of the claim.

Finally, when evaluating the scope of a claim, every limitation in the claim must be considered. USPTO personnel may not dissect a claimed invention into discrete elements and then evaluate the elements in isolation. Instead, **the claim as a whole must be considered.** See, e.g., *Diamond v. Diehr*, 450 U.S. 175, 188-89, 209 USPQ 1, 9 (1981).

Accordingly, rather than requiring that the claims are insolubly ambiguous, the Board of Patent Appeals and Interferences has stated in a rare precedential opinion that the "USPTO is justified in using a lower threshold showing of ambiguity to support a finding of indefiniteness under 35 U.S.C. § 112, second paragraph, because the applicant has an opportunity and a duty to amend the claims during prosecution to more clearly and precisely define the metes and bounds of the claimed invention and to more clearly and precisely put the public on notice of the scope of the patent." *Ex parte Miyazaki*, Appeal 2007-3300, November 19, 2008, at p. 12.

With regard to § 112, second paragraph, M.P.E.P. § 2171 states that there are two separate requirements set forth in this paragraph: the claims must set forth the subject matter that applicants regard as their invention; and the claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant.

With further regard to the first requirement set forth under § 112, second paragraph, M.P.E.P. § 2171 states the determination of the sufficiency of the claim to satisfy that requirement is subjective because it is dependent on what the applicant for a patent regards as the invention. As that is the case, it is important to note instances in which Applicant's remarks suggest that their invention is something other than which is claimed because such remarks constitute evidence that shows that a claim does not correspond in scope with that which applicant regards as applicant's invention<sup>4</sup>. Furthermore, M.P.E.P. § 2173 states that a clear measure of what an applicant regards as the invention is necessary so that it can be determined whether the claimed invention meets all the criteria for patentability and whether the specification meets the criteria of 35 U.S.C. 112, first paragraph with respect to the claimed invention.

With further regard to the second requirement, M.P.E.P. § 2173 states "[in] reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph, by providing clear warning to others as to what constitutes infringement of the patent".

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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<sup>4</sup> See M.P.E.P. § 2172 (II).

13. The rejection of claims 10-19, 29, and 30 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Beginning at page 12 of the amendment filed September 17, 2009, Applicant has traversed the propriety of maintaining this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

This is a "written description" rejection.

As noted previously, the considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, "Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereinafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsius verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

*Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). See also: *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention*.

In this instance, the claims are directed to a method of treating a "cancer regulated by HER-kinase axis activation that is resistant to therapeutic treatments directed exclusively at either the PPAR-gamma pathway or the HER-kinase axis" in a mammal, said method comprising administering a quantity of a non-steroidal anti-inflammatory drug (NSAID) that "modulates the PPAR-gamma pathway" and a quantity of a "HER2-kinase axis inhibitor", both on a periodic basis.

(a) As presently amended, the claims are directed to a genus of "cancers", which are too inadequately described with the requisite clarity and particularity to permit the skilled artisan to immediately envision, recognize or distinguish at least a substantial number of the members of this genus, so as to know when the invention can or cannot be used to achieve the claimed objective. As a consequence the disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Moreover, as explained in the new matter rejection that follows, it appears that there may be inadequate written support for the language of the present claims since the specification, as originally filed, fails to describe "resistant" cancer, or more particularly the genus of cancers that are "regulated by HER-kinase axis activation that is resistant to therapeutic treatments directed exclusively at either the PPAR-gamma pathway or the HER-kinase axis". At paragraph [0008] of the published application<sup>5</sup>, the specification discloses: "A significant limitation in therapeutic treatments directed exclusively at either the PPAR $\gamma$  pathway or the HER-kinase axis is that recipients thereof tend to develop a resistance to their therapeutic effects after they initially respond to therapy"; this disclosure however does not described the claimed invention and it does not describe with any clarity or particularity the specific nature of the therapeutic treatments directed exclusively at either the PPAR $\gamma$  pathway or the HER-kinase, so as to enable the skilled artisan to immediately know or recognize such treatments.

At paragraph [0001], for example, of the published application, the specification discloses that "[e]mbodiments of the present invention are directed to methods for treating and preventing disease conditions that are modulated by the PPAR $\gamma$  pathway and HER-kinase axis, such as cancer", but not necessarily of the claimed genus of cancer, which is "regulated by HER-kinase axis activation that is resistant to therapeutic treatments directed exclusively at either the PPAR-gamma pathway or the HER-kinase axis".

Certainly not all types of cancer are or should be considered to be "regulated by HER-kinase axis activation that is resistant to therapeutic treatments directed exclusively at either the PPAR-gamma pathway or the HER-kinase axis", but since the disclosure fails to describe such cancer it is not evident which features characterize the types of cancer to which the claims are directed.

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<sup>5</sup> U.S. Patent Application Publication No. 2007/0104714 A1.

Dorland's Illustrated Medical Dictionary<sup>6</sup> defines the term "cancer" as meaning "any malignant, cellular tumor, referring to neoplastic diseases in which there is a transformation of normal body cells into malignant ones"; wherein the term "tumor" is defined as: "a new growth of tissue in which cell multiplication is uncontrolled and progressive"; and the term "malignant" is defined as: "having the properties of anaplasia, invasiveness, and metastasis" (Copyright © 2007 Elsevier; Copyright © 2002-2008 Merck & Co., Inc., Whitehouse Station, NJ, USA).

Notably cancer is not defined in such a manner that it is evident that it is necessarily a disease that is modulated by the PPAR $\gamma$  pathway and HER-kinase axis, nor is it evident that cancer should always be thought of as a disease that is "regulated by HER-kinase axis activation that is resistant to therapeutic treatments directed exclusively at either the PPAR-gamma pathway or the HER-kinase axis".

To the contrary, as before noted, cancer is a term that is used to describe any of a large number of diseases affecting a multitude of different cells and/or tissues; and such different types of cancer have markedly different etiologies and pathologies.

The specification describes the "cancer" to which the cells are directed to be inclusive of "prostate cancer", for example; yet, it is not evident how "prostate cancer" might be fairly regarded as representative of the genus of "cancers" that are treated using the claimed invention because it is not immediately evident how prostate cancer and any other member of the claimed genus of "cancers" are "modulated by the PPAR $\gamma$  pathway and HER-kinase axis", particularly since it is not clear what constitutes the pathway or the "axis", or by what nature or manner either the pathway or axis, or constituents thereof, modulate the condition.

There is simply no means of knowing which types of cancer are those to which the claims are directed, and which are not, apart from empirically determining if any given type of cancer is "resistant to therapeutic treatments directed exclusively at either the PPAR-gamma pathway or the HER-kinase axis", but in order to do that one would

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<sup>6</sup> Available on the Internet at:  
[http://www.mercksource.com/pp/us/cns/cns\\_hi\\_dorlands\\_split.jsp?pg=/ppdocs/us/common/dorlands/dorland/two/000016439.htm](http://www.mercksource.com/pp/us/cns/cns_hi_dorlands_split.jsp?pg=/ppdocs/us/common/dorlands/dorland/two/000016439.htm).

first have to know which therapeutic treatments are directed exclusively at either the PPAR-gamma pathway or the HER-kinase axis and which types of cancer are regulated by "HER-kinase axis activation".

Applicant is again reminded that "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

"Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1894 (CAFC 2004). The claimed method depends upon finding a sample of the "cancer" that is suitable for use in practicing the claimed invention to achieve the claimed objective; without such a sample, it is impossible to practice the invention.

There is no means of knowing whether the claimed invention can be used to treat any given type of "cancer", and thus achieve the claimed objective, if the "cancer" that must be treated cannot be not known or recognized; moreover, there is simply no way to predict which of the multitude of etiologically and/or pathologically disparate types of cancer to which the claims might broadly, but reasonably directed in light of the disclosure, are those that are effectively treated in accordance with the process steps recited in the claims.

Although this issue is addressed again in the following paragraphs, it is aptly noted that the Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568).

Accordingly, the specification fails to describe the claimed genus of "cancers" with the requisite clarity and particularity to permit the skilled artisan to immediately

envision, recognize or distinguish at least a substantial number of the members of this genus.

Finally, although the skilled artisan could potentially identify the different types of cancer that might be applicable in the practice of the claimed invention by establishing which can be treated using the combination of agents to which the claims are directed, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

*Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). *See Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

So, in summary, as a consequence of the inadequate description of the genus of "cancers" to which the claims are directed, the disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Applicant has argued that the claims, as presently amended, are adequately supported by the disclosure; however for reasons explained in the paragraphs above this is not the case.

(b) As another point to be addressed, it is further noted that the claims are drawn to a quantity of a non-steroidal anti-inflammatory drug (NSAID) and a quantity of a "HER2-kinase axis inhibitor".

With regard to the written description requirement, it is pertinent that terms used in the claims to describe the agents that are administered to the mammal serve to identify the agents with clarity and particularity.

Although non-steroidal anti-inflammatory agents (NSAIDs) are well known in the art<sup>7</sup>, it is submitted that the genus of "HER2-kinase axis inhibitors" is not.

According to paragraph [0027] of the published application, the "HER2-kinase axis inhibitor" is any of a number of structurally and/or functionally unrelated agents, including, for example, a monoclonal antibody, rapamycin, or a tyrosine kinase inhibitor.

Notably, the monoclonal antibody need not bind any particular antigen; and the tyrosine kinase inhibitor need not inhibit the activity of any particular kinase.

Given that members of genus of "HER2-kinase axis inhibitors" have such different structures and/or functions, it is submitted that the skilled artisan could not immediately envision, recognize or distinguish at least a substantial number of the different agents to which the claims are directed.

Despite some non-limiting guidance in paragraph [0027] of the published application, for example, it is not evident which structural and/or functional features serve to identify the "HER2-kinase axis inhibitor", or which structural and/or functional features serve to distinguish members of genus of such agents from others.

Even in light of the disclosures at paragraph [0027], for example, of the published application, it is submitted that the "HER2-kinase axis inhibitors" that are used in practicing the claimed invention are not adequately described with the requisite clarity and particularity to permit the skilled artisan to know which agents those are.

While the written description requirement can be satisfied without an actual reduction to practice, the disclosure of a catalog of "HER2-kinase axis inhibitors" that might be applicable in practicing the claimed invention to achieve the claimed objective does not fulfill the written description requirement.

Notably, the Federal Circuit has decided that a generic statement that defines a genus of substances by *only* their functional activity, e.g., the ability to treat a condition, does not provide an adequate written description of the genus. See *The Reagents of*

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<sup>7</sup> A NSAID is defined by Dorland's Illustrated Medical Dictionary (available on the Internet at [http://www.mercksource.com/pp/us/cns/cns\\_hl\\_dorlands\\_split.jsp?pg=/ppdocs/us/common/dorlands/dorland/misc/dmd-a-b-000.htm](http://www.mercksource.com/pp/us/cns/cns_hl_dorlands_split.jsp?pg=/ppdocs/us/common/dorlands/dorland/misc/dmd-a-b-000.htm)) as meaning "any in a large group of drugs that are analgesic (pain-reducing), antipyretic (fever-reducing), and antiinflammatory (inflammation-reducing)" (Copyright © 2007 Elsevier; Copyright © 2002-2008 Merck & Co., Inc., Whitehouse Station, NJ, USA).

*the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1894 (CAFC 2004).

The claimed method depends upon finding a "HER2-kinase axis inhibitor" that can be used in the practice of the claimed invention, so that the claimed objective might be met; without the "HER2-kinase axis inhibitor", it is impossible to practice the invention.

Guidelines states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of "HER2-kinase axis inhibitors", which vary both structurally and functionally, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant

has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

Apart from any of the particularly described "HER2-kinase axis inhibitors" (e.g., rapamycin), the disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed genus of agents, or of the claimed invention.

It is submitted that the genus of "HER2-kinase axis inhibitors" to which the claims are directed is too inadequately described to satisfy the written description requirement.

Then, with regard to the NSAIDs to which the claims are directed, although the prior art describes a large number of such drugs, many of those are not the equivalents of others, having different structures and/or functions, including, for example, different selectivities in terms of their abilities to inhibit either cyclooxygenase-1 (COX1) or cyclooxygenase-2 (COX2), or both COX1 and COX2, so it is not immediately evident which NSAIDs can be used in combination with the "HER2-kinase axis inhibitors" to treat a condition, particularly since the "conditions" that are treated are so very different. It stands to reason that only some NSAIDs might be used effectively in combination with only some members of the genus of "HER2-kinase axis inhibitors" to treat only some of the conditions to which the claims are directed.

For all of these reasons, it is submitted that the claims fail to satisfy the written description requirement, since the disclosure of the claimed invention would not reasonably convey to the skilled artisan that Applicant had possession of the claimed subject matter at the time the application was filed.

Applicant has further argued that the term "HER-kinase axis inhibitor" is a well known description used in the art; yet, the term is not included in any known dictionary and appears only in one reference published by Applicant in June 2004 (i.e., Hedvat et al., which is of record).

Applicant has argued that the skilled artisan is able to envision, recognize or distinguish at least a substantial number of members of the claimed genus of "HER-kinase axis inhibitor"; yet, as explained, it is not evident which structure and/or functional features characterize those substances that are. Considering the vast

structural and functional differences of the members of the genus that are recited in the Markush group of claim 12 it is clear that there is no one particularly identifying structural or functional feature that is common to at least a substantial number of its members. As such, it is beyond comprehension how the skilled artisan is able to envision, recognize or distinguish at least a substantial number of members of the claimed genus of "HER-kinase axis inhibitor".

Applicant has argued that it is inappropriate to consider which NSAIDs are used to practice the invention, so as to achieve the claimed therapeutic effect, and which are not, or whether those NSAIDs that might be effectively used have been adequately described. In response, as explained, "[r]egardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1894 (CAFC 2004). Thus, this issue is indeed relevant to a determination that the written description requirement has been met by the disclosure in this application. The claimed method depends upon finding an NSAID that can be used in combination with a "HER-kinase axis inhibitor", so as to be suitable for use in practicing the claimed invention to achieve the claimed objective; presumably it will not be any NSAID that is so suitable, and without the drug, it is impossible to practice the invention.

In this case, since the claims are so broad, and the disclosure is so comparably limited, it is submitted that any alleged conception has no more specificity than simply a wish to know the identity of any materials with that requisite pharmacologic properties, which can be used to practice the claimed processes, so as to achieve the claimed objectives or effects.

In such instances, the alleged conception fails not merely because the field is unpredictable or because of the general uncertainty surrounding experimental sciences, but because the conception is incomplete due to factual uncertainty that undermines the specificity of the inventor's idea of the invention. *Burroughs Wellcome Co. v. Barr*

*Laboratories Inc.*, 40 F.3d 1223, 1229, 32 USPQ2d 1915, 1920 (Fed. Cir. 1994). Reduction to practice in effect provides the only evidence to corroborate conception (and therefore possession) of the invention.

Lastly, since the claims are not necessarily limited to known materials having the properties of the combination of a "HER-kinase axis inhibitor" and a "NSAID", but rather to such material that might be identified, given the bid set forth in the instant disclosure to do so, it is noted that one cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483 (Bd. Pat. App. & Int. 1993).

Thus, it is submitted that the instant claims, and the disclosure describing the claimed subject matter, fails to satisfy the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

14. The rejection of claims 10-19, 29, and 30 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Beginning at page 13 of the amendment filed September 17, 2009, Applicant has traversed the propriety of maintaining this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

As before noted, M.P.E.P. § 2164.01 states:

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

Largely for the same reasons explained in the preceding Office action, it is submitted that the amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

As explained in the above rejection of the claims under 35 U.S.C. § 112, first paragraph, the claims are directed to a method of treating a "cancer regulated by HER-kinase axis activation that is resistant to therapeutic treatments directed exclusively at either the PPAR-gamma pathway or the HER-kinase axis" in a mammal, said method comprising administering a quantity of a non-steroidal anti-inflammatory drug (NSAID) that "modulates the PPAR-gamma pathway" and a quantity of a "HER2-kinase axis inhibitor", both on a periodic basis.

As explained previously, given the vast differences in the breadth of the claims and that of the guidance, direction and exemplification that is set forth in this application, it is apparent that the claimed process could not be practiced without undue and/or unreasonable experimentation.

While there are a great many reasons that this is the case, among such reasons, it is noted that the claims are directed to a "HER2-kinase axis inhibitors", which are not known or disclosed; and it cannot be predicted which agents can and cannot be

considered "HER2-kinase axis inhibitors". Without that knowledge the "HER2-kinase axis inhibitor" the claimed invention cannot be used.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

Thus, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to elaborate upon the disclosure to develop a process that is encompassed by the claims, which can be used as intended to treat a condition using a combination of a NSAID and this other substance that has been termed the "HER2-kinase axis inhibitor".

Defining a substance by its principal biological activity, or its suitability for use in practicing the claimed process amounts to an alleged conception having no more specificity than that of a wish to know the identity of any material with that biological property. See *Colbert v. Lofdahl*, 21 USPQ2d 1068, 1071 (BPAI 1991).

The propriety of this ground of rejection is supported by the following discussion, which is an excerpt from the rejection set forth in the preceding Office action.

As explained in the above rejection of the claims as failing to satisfy the written description requirement, it is submitted that apart from any of the particularly described "HER2-kinase axis inhibitors" (e.g., rapamycin), the disclosure fails to adequately describe these agents; of course, what has not been described cannot be made; and then what cannot be made cannot be used, certainly not without undue and unreasonable experimentation.

So can rapamycin, for example, be used in combination with a NSIAD to treat a condition?

The only disclosure that is specifically relevant to this embodiment of the claimed invention is that of the original claim 12 and the paragraph at page 13, lines 8-30, which lists rapamycin along with the generic monoclonal antibody lacking any particular binding specificity as examples of the agents that might be used as "HER2-kinase axis inhibitors".

There is no other disclosure in the specification that pertains to this embodiment.

The use of this embodiment has not been exemplified.

Rapamycin (sirolimus) is an immunosuppressive macrolide antibiotic with structural similarity to FK506, which inhibits T- and B-cell proliferation at a later stage than FK506. More particularly, rapamycin inhibits mTOR, which participates in the Ras/MAP kinase signaling pathway. Rapamycin inhibits mTOR by through association with its intracellular receptor FKBP12. Because of its immunosuppressive properties, rapamycin has been used to prevent rejection of organ and bone marrow transplants by the body; however, because mTOR regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, and transcription via the Ras/MAP signaling pathway, recent investigations have explored the effectiveness of rapamycin in treating cancer.

While it may be obvious to combine rapamycin with any other anticancer agent (e.g., a NSAID) to determine if the combination is more effective than either agent alone to treat a given condition<sup>8</sup>, there does not appear to be any indication in the prior art that the combination of rapamycin and any particular NSAID should be used to treat cancer, for example, or graft versus host disease or any other condition; and, as mentioned, the specification, provides little or no guidance and direction, apart from the mere disclosure that rapamycin may be considered a member of the genus of "HER2-kinase axis inhibitors" to which the claims are directed.

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<sup>8</sup> It is *prima facie* obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition that is to be used for the very same purpose. The idea of combining the first and second compositions to form a third flows logically from having the first and second been individually taught in the prior art. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980); see M.P.E.P. § 2144.06.

Only recently have any investigations provided actual data indicating that the combination of rapamycin and a NSAID, namely celecoxib (an inhibitor of COX2) has additive antitumor effects (i.e., the combination of drugs more effectively inhibit melanoma cell growth than either drug alone)<sup>9</sup>. However, Applicant is reminded that supporting documents cannot be relied upon to correct the deficiencies of the specification by supplying the necessary and essential teachings, guidance, and exemplification that the specification lacks. See M.P.E.P. § 2164.05(a).

Similarly, while there may indeed be recently acquired evidence that certain combinations of a particularly described member of the genus of "HER2-kinase axis inhibitors" (e.g., monoclonal antibody 2C4; gefitinib; and imatinib mesylate) and a NSAID are effective to treat conditions or diseases, which are generally different types of cancer, it appears that the specification, at best, might only provide guidance and direction sufficient to reasonably enable the skilled artisan to treat prostate cancer with a regimen of the NSAID, R-etodolac in combination with recombinant humanized monoclonal anti-HER2 antibody 2C4 (rh2C4); see, e.g., paragraphs [0076] of the published application. However, none of the claims are so limited, and since such a showing is most certainly not reasonably commensurate in scope with far broader claims, which are directed to a method of treating any "condition", not prostate cancer, by administering to a mammal afflicted with this condition an amount of any "non-steroidal anti-inflammatory drug", not R-etodolac, and an amount of a "HER2-kinase axis inhibitor", not rh2C4, the amount of guidance, direction and exemplification would not be adequate to enable the skilled artisan to use the claimed invention without undue and unreasonable experimentation.

It is important to note that not all NSAIDs act in the same ways; some are inhibitors of COX2, but others are not; and some are trans-activators of PPAR $\gamma$ , but others are not. Thus, if R-etodolac acts in concert with the "HER2-kinase axis inhibitor" by trans-activating PPAR $\gamma$ <sup>10</sup> to more effectively inhibit the growth of prostate cancer

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<sup>9</sup> Bundscherer et al. (*Oncol. Rep.* 2008 Feb; **19** (2): 547-553); see entire document (e.g., the abstract).

<sup>10</sup> R-etodolac does not inhibit COX2.

cells, then it follows that not all NSAIDs can be paired with a "HER2-kinase axis inhibitor" and expected to be produce additive antitumor effects.

S-etodolac, the entantiomer of R-etodolac selectively inhibits COX2, whereas R-etodolac does not. Thus, despite having such similar structures, the enantiomers have markedly different activities.

Can it be presumed that the disclosed process for inhibiting prostate cancer cells can be used, as claimed, by substituting S-etodolac for R-etodolac or any other NSAID?

Hedvat et al. (*Cancer Cell* 2004 Jun; 5: 565-574) teaches that S-etodolac is capable of trans-activating PPAR $\gamma$ , but to significantly lower levels; see entire document (e.g., the abstract).

Might not the much poorer ability of S-etodolac to trans-activate PPAR $\gamma$  cause the drug to act ineffectively in combination with the "HER2-kinase axis inhibitor", or might not the combination be no more effective than either one of the agents alone?

The answers to these questions are not provided in the disclosure; and the skilled artisan has no means by which the outcomes may be predicted.

In each case, the outcome of using different combinations of a NSAID and a "HER2-kinase axis inhibitor" must be determined empirically in pre-clinical or clinical trials.

Of course, since drugs often have many different effects and mechanisms of action, it is entirely possible that the antitumor activity of R-etodolac results from an effect that is independent of its ability to trans-activate PPAR $\gamma$ .

Curcumin (diferuloylmethane), for example, has been shown to act in combination with other antitumor drugs. Curcumin might be considered a "pharmaceutical equivalent" of the NSAID to which the claims are directed since it inhibits the activity of COX2 and trans-activates PPAR $\gamma$ , but curcumin has also been shown to inhibit the activation of mTOR and NF-kappaB.

Might not one of the other specific activities of a NSAID, such as curcumin account for any additive or synergistic effect that might be observed when used in combination with any given member of the genus of "HER2-kinase axis inhibitor"?

How can one know without first performing a series of highly complex experiments?

Regardless of the answer, it is apparent that the claimed invention cannot be practiced to achieve the claimed objective without undue and unreasonable experimentation.

Notably, too, there are substantial overlaps in the effects that are produced by members of the genus of "HER2-kinase axis inhibitors" and the different NSAIDs to which the claims are directed, which further blurs the features that might serve to guide the artisan to select a combination that is used effectively to treat a condition. For example, both curcumin, an agonist of PPAR $\gamma$ , and a presumed functional equivalent of the claimed NSAID, and rapamycin act to inhibit the activation of mTOR; but numerous other similarities have been noted, which cause the Examiner to ponder whether the claim might not be anticipated by a showing in the prior art that administering a single therapeutic agent having properties of both the "NSAID" and the "HER2-kinase axis inhibitor" treats a condition.

Nonetheless, it is for the reasons set forth in the paragraphs above that Applicant is reminded of the following:

It is well known that the art of drug discovery for is highly unpredictable. With particular regard to anticancer drug discovery, Gura (*Science*. 1997; **278**: 1041-1042), for example, teaches that researchers are faced with the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile (abstract). Because of a lack of predictability, Gura discloses that often researchers merely succeed in developing a therapeutic agent that is useful for treating the animal or cell that has been used as a model, but which is ineffective in humans, and indicates that the results acquired during pre-clinical studies are often non-correlative with the results acquired during clinical trials (page 1041, column 2). Gura very succinctly teaches our lack in ability to reliably extrapolate pre-clinical data to accurately predict the outcomes of such treatments in humans is due to the fact that "xenograft tumors don't behave like naturally occurring tumors in humans" (page 1041, column 2). Gura teaches that although researchers had hoped that xenografts would

prove to better models for studying cancer in humans and screening candidate therapeutic agents for use in treating patient diagnosed with cancer, "the results of xenograft screening turned out to be not much better than those obtained with the original models". Gura states that as a result of their efforts, " [w]e had basically discovered compounds that were good mouse drugs rather than good human drugs' ".

Saijo et al. (*Cancer Sci.* 2004 Oct; **95** (10): 772-776) recently reviewed the reasons for negative phase III trial of molecular-target-based drugs and their combinations; see entire document (e.g., the abstract). Saijo et al. discloses that while numerous phase III trials have been conducted upon the basis of promising preclinical data such as that disclosed in the instant application, few have yielded strongly positive results, and the majority of results have been negative (e.g., abstract). Saijo et al. discloses that there are problems in preclinical prediction of combined effects of anticancer drugs, and the results of preclinical prediction of combined effects have been very poor (page 773, column 2). Saijo et al. teaches many reasons for the poor predictability of combined effects (page 774, Table 6).

Kelland (*Eur. J. Cancer.* 2004 Apr; **40** (6): 827-836) has reviewed the reliability of the model in predicting clinical response; see entire document (e.g., the abstract). While the successful use of such models in cytotoxic drug development is conclusive, Kelland discloses that today there is far less focus on the development of such drugs (page 833, column 2); rather, the focus is upon the development of "molecularly-targeted", largely cytostatic drugs, such as those disclosed in the instant application, which may act in synergy with other drugs to selectively reduce or inhibit the growth of neoplastic cells (e.g., page 885). In particular, where such drugs are naked humanized antibodies that act through mechanisms such as ADCC, Kelland states the models are of limited value, because such mechanisms depend upon the recruitment of the host's (i.e., mouse) immune response, which differs from or is not reflective of that found in man (page 834, column 2). With such limitations of the xenograft model in mind, Kelland suggests that the case for using the model within a target-driven drug development cascade need to be justified on a case-by-case basis (page 835, column 1). Still, Kelland et al. does not altogether discount the usefulness of such models,

since, at present, "it is premature and too much a 'leap of faith' to jump directly from *in vitro* activity testing (or even *in silico* methods) to Phase I clinical trials (via preclinical regulatory toxicology)" (page 835, column 2). Kelland, however, does not advocate the use of a single xenograft model to exhort one to accept assertions of the effectiveness of treating multiple and different diseases using the same agent, as has been done in the instant application, since Kelland compels one to decide on a case-by-case basis whether such a model is suitable or not.

Bergers et al. (*Current Opinion in Genetics and Development*. 2000; **10**: 120-127) comments upon the inability to extrapolate preclinical data to reliably predict the outcome of treating humans using drugs tested in mice, particularly matrix metalloproteinase inhibitors. Bergers et al. teaches:

A body of data over the past few years indicate [...] that proteinases and proteinase inhibitors may, under special circumstance, either favor or block tumor progression. For example, ectopic expression of TIMP-1 [a natural inhibitor of metalloproteinases] allows for some tumors to grow, while inhibiting others" (page 125, column 2).

In fact, Bergers et al. discloses that the Bayer Corporation recently halted a clinical trial of a metalloproteinase inhibitor because patients given the drug experienced greater progression of cancer than did patients given a placebo (page 125, column 1). Bergers et al. comments, "these results are somewhat surprising and contrary to Bayers' preclinical data, which confirmed that the drug inhibited tumor activity in rodents" (page 124, paragraph bridging columns 1 and 2).

Most recently, Dennis (*Nature*. 2006 Aug 7; **442**: 739-741) reports, despite their present indispensableness, mouse models, such as xenografts, have only limited utility in predicting the clinical effectiveness of anticancer treatments; see entire document (e.g., page 739, column 2). Dennis explains there is a "laundry list" of problems associated with the use of mice to model human diseases, such as cancer (page 739, column 1). Accordingly, Dennis reports, "[a]lthough virtually every successful cancer drug on the market will have undergone xenograft testing, many more that show positive results in mice have had little or no effect on humans, possibly because the human tumours are growing in a foreign environment" (page 740, column 1). Therefore,

quoting Howard Fine, Dennis concludes: " 'Mice are valuable but they are, after all, still mice' ", suggesting the best study subject will always be the human (page 741, column 3).

Thus, the skilled artisan cannot accurately and reliably predict the effect of administering a pharmaceutical composition comprising an agent purported to have a desired pharmacological effect to a subject. Always the therapeutic effectiveness or efficacy of any unproven drug regimen can only be determined empirically.

Applicant has argued that one of ordinary skill in the art would recognize agents that to be used in practicing the claimed invention so as to achieve the claimed therapeutic objective; yet, since the claims are not necessarily directed to know compounds that have the ability to act in concert with one another to treat any of the different types of cancer to which the claims are directed that is clearly not the case. Moreover, as already explained in this Office action and in the preceding Office action, the skilled artisan could not immediately envision, recognize or distinguish the claimed "HER-kinase axis inhibitors" and "NSAIDs" that are used to practice the claimed invention; if so, the claimed invention cannot be so adequately described by the specification to permit the skilled artisan to use the invention without undue and unreasonable experimentation since it would first be necessarily to identify the "HER-kinase axis inhibitors" and "NSAIDs" that are used to practice the claimed invention in order to treat any of the many different types of cancer to which the claims are directed.

Applicant has argued that the role of the "HER-kinase axis" in cancer is well documented; but as explained it is not even apparent which cellular components as part of this "axis", and which do not. Again, what is the "HER-kinase axis"? Where has it been described apart from Applicant's publication (i.e., Hedvat et al.)? Obviously if one does not know which types of cancer are treated with the claimed invention, it cannot be used without undue and unreasonable experimentation since it would first be necessarily to identify types of cancer that are effectively treated using the combination of the drugs to which the claims are directed.

In this instance because the claims are so vague and indefinite and use unconventional terminology that is not expressly defined in the application it is nearly

impossible to surmise which if any subject matter encompassed by the claims is in fact reasonably enabled; so again Applicant reminded that reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enabled the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

#### ***Claim Rejections - 35 USC § 102***

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. The rejection of claims 10-12 under 35 U.S.C. 102(b), as being anticipated by Mitsiades et al. (*Semin. Oncol.* 2003 Apr; 30 (2): 309-312), is maintained.

Beginning at page 15 of the amendment filed September 17, 2009, Applicant has traversed the propriety of maintaining this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Here, the claims are drawn to a process of treating Waldenstrom's macroglobulinemia, said process comprising administering to a human afflicted with the condition a quantity of a peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) agonist and a quantity of an ansamycin.

Absent a showing of any difference, a PPAR $\gamma$  agonist, such as R-etodolac or rosiglitazone, is deemed the same as a non-steroidal anti-inflammatory drug (NSAID) or pharmaceutical equivalent thereof. This position is supported throughout the specification, which discloses, for example, that the NSAID is "R-etodolac or a R-etodolac derivative, but may also include, without limitation, [...] pharmaceutical equivalents, derivatives and salts, as well as other functionally related compounds" (paragraph [0026] of the published application) and that R-etodolac activates PPAR $\gamma$  (e.g., paragraph [0026] and [0066]-[0070] of the published application).

Mitsiades et al. teaches a process of treating Waldenstrom's macroglobulinemia (WM), said process comprising administering to a human afflicted with the condition a quantity of a peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) agonist, such as ciglitazone or rosiglitazone) and a quantity of an ansamycin, such as geldanamycin and its analogues; see entire document (e.g., the abstract). Mitsiades et al. teaches their preclinical data show that these classes of agents induce growth arrest and apoptosis of WM cells, and at concentrations relevant to those achieved in previous clinical uses of these same drugs (abstract).

Although the claims recite a limitation that the agents are administered on a "periodic basis", according to the specification, "periodically," as used in this application, "includes, but is in no way limited to, any interval of time" (paragraph [0035] of the published application). Then, the terms "NSAID periodic basis" and "HER-kinase axis inhibitor periodic basis" are consistently defined to mean including, but is in no way limited to any interval of time as would be recognized by one skilled in the art (paragraph [0035] of the published application). As such, the recitation of the limitation has little effect in defining the subject matter that is encompassed by the claims since the agents might be administered only once, or more than once at any given interval of time, and either together or separately; but then few treatment regimens involve the single administration of one or another drug, either when used alone or in combination, so it is expected that any appropriate interval of time between repeated administrations

of the drugs described by the prior art would, in fact, be recognized by one skilled in the art.

Notably Applicant has argued that neither ciglitazone nor rosiglitazone are non-steroidal anti-inflammatory drugs (NSAIDs).

In response, in accordance with claim 11 (as originally presented), for example, the NSAID to which the claims are directed is a derivative, analog, or pharmaceutical equivalent of any of the other drugs that are recited in the Markush group. Thus, both ciglitazone and rosiglitazone are rightly considered NSAIDs since each is a derivative, analog, or pharmaceutical equivalent of one or more of the other drugs that is recited in the Markush group.

Then, as to whether or not ciglitazone and rosiglitazone are NSAIDs that "modulate the PPAR-gamma pathway", it is aptly noted that the specification discloses: "One therapeutic treatment known to act on the PPAR $\gamma$  is the group of non-steroidal anti-inflammatory drugs, otherwise known as 'NSAIDS' " (paragraph [0006] of the published application). Thus, in accordance with this disclosure, the NSAID is a drug that "modulates the PPAR-gamma pathway".

Applicant has further argued that the prior art does not teach the treatment of "resistant cancer".

In response, it is unclear why Applicant has argued that the prior does not teach the treatment of "resistant cancer", but presumably Applicant intended to argue that WM is not the type of cancer to which the claims are directed. The claims, as presently amended, are directed to a method of treating a cancer regulated by HER-kinase axis activation that is resistant to therapeutic treatments directed exclusively at either the PPAR-gamma pathway or the HER-kinase axis", but Applicant has failed to provide any factual evidence that might support an assertion that Waldenström's macroglobulinemia (WM) is not such a cancer; and contrary to any such assertion, WM has been described as a "resistant cancer"<sup>11</sup>. In fact, though Mitsiades et al. may not teach WM is a

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<sup>11</sup> See, e.g., Anagnostopoulos et al. (*Bone Marrow Transplant.* 2001 May; **27** (10): 1027-1029). Anagnostopoulos et al. discloses that treatment of WM with alkylating agents induces a partial response in approximately 50% of patients, while the response rate to nucleoside analogues has been

"resistant cancer", Mitsiades et al. does disclose that WM "remains an incurable B-cell malignancy, necessitating urgent development of novel treatment strategies" (abstract), such that it clear that WM is in fact a type of cancer that is "resistant" to current or conventional therapies.

As to whether WM is resistant to "therapeutic treatments directed exclusively at either the PPAR-gamma pathway or the HER-kinase axis", first it is unclear which therapies those are, and which therapies they are not. This is certainly the case since most drugs are likely to lack the specificity and selectivity that is required by the claims and it seems doubtful that any antitumor treatment should be considered to be directed *exclusively* at either the PPAR-gamma pathway or the HER-kinase axis, especially since it cannot be ascertained which molecular targets are components of the pathway or the axis, and which are not. So, if Applicant might not consider WM a type of cancer that is resistant to treatment using a drug that is directed "exclusively at either the PPAR-gamma pathway or the HER-kinase axis", it is submitted that the claims fail to clearly and particularly point out the specific features of the drugs which are, such that it is possible to distinguish that which is claimed from that which is taught by the prior art. Secondly, the Office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics as the cancer to which the claims are directed. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the cancer to which the claims are directed is different than that taught by the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977) and *Ex parte Gray*, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

Thus, although Applicant's arguments have been carefully considered, absent a showing of any difference, it is submitted that the claimed process is anticipated by the the prior art, which teaches a process of treating Waldenström's macroglobulinemia

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approximately 80%; but nevertheless, as Anagnostopoulos et al. further discloses, complete responses are rare (page 1027, column 1). Moreover, Anagnostopoulos et al. describes a study in which each participant was afflicted with resistant disease (page 1027, column 2).

(WM), said process comprising administering to a human afflicted with the condition a quantity of a peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) agonist, such as ciglitazone or rosiglitazone) and a quantity of an ansamycin, such as geldanamycin and its analogues.

17. The rejection of claims 10-19 and 29-33 under 35 U.S.C. 102(a)<sup>12</sup>, as being anticipated by Hedvat et al. (*Cancer Cell*. 2004 Jun; 5: 565-574), is maintained.

Beginning at page 15 of the amendment filed September 17, 2009, Applicant has traversed the propriety of maintaining this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Here, the claims are drawn to a process of treating prostate cancer, said process comprising administering to a mammal afflicted with the condition a quantity of R-etolodac and a quantity of antibody 2C4.

Hedvat et al. teaches treating prostate cancer by administering to a mammal afflicted with the condition a quantity of R-etolodac and a quantity of a recombinant humanized antibody, which is designated 2C4; see entire document (e.g., the abstract). Hedvat et al. teaches the combination regimen consisted of daily administration of 200 mg/kg R-etolodac by oral gavage and twice weekly administration of 20 mg/kg antibody 2C4 by intraperitoneal injection; see, e.g., page 572, column 1.

Applicant has argued that Hedvat et al. is not prior art under § 102(b), which is true, but as Applicant is aware since the reference describing the claimed invention was published by an entity other than the inventive entity before the filing date of the instant application it is prior art under § 102(a).

### ***Claim Rejections - 35 USC § 103***

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

19. The rejection of claims 10 and 15-19 under 35 U.S.C. 103(a), as being unpatentable over Mitsiades et al. (*Semin. Oncol.* 2003 Apr; 30 (2): 309-312), is maintained.

Beginning at page 16 of the amendment filed September 17, 2009, Applicant has traversed the propriety of maintaining this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Mitsiades et al. teaches that which is set forth in the above rejection of claims 10-12 under 35 U.S.C. § 102(b), but does not address the specific regimen according to which the drugs are administered, nor expressly suggests that the quantity of the peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) agonist is from about 100 to about 500 mg/kg of the mammal, or that it is administered daily, or that the quantity of the ansamycin is from about 100 to about 500 mg/kg, or that each drug is administered twice weekly, or that it is administered twice weekly.

The claims, however, are not limited to any one particular drug, but rather to a class of drugs having equivalent functions; and similarly the prior art teaches the effectiveness of combinations of different classes of drugs to treat the condition. In light of such permissible variance, it seems that the doses, schedules, and routes of delivery that are used in practicing the process that is claimed, and the process that is disclosed by the prior art, will vary.

It is a common objective in the art to establish a dose, schedule, and route of delivery that is both safe and effective, so as achieve optimal therapeutic effect and maximal benefit. See *In re Boesch*, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980) ("[D]iscovery of an optimum value of a result effective variable in a known

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<sup>12</sup> As Applicant correctly noted in their response filed September 17, 2008, this same ground of rejection was erroneously set forth under 35 U.S.C. § 102(b) in the preceding Office action.

process is ordinarily within the skill of the art.” (citations omitted)). See In re Peterson, 65 USPQ2d 1379 1382 (CA FC 2003): “The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.”

Then, with particular regard to claim 19, although the prior art does not expressly teach how each agent is administered, it is evident that the agents are delivered in accordance with their prior clinical uses, as discussed by Mitsiades et al., which absent a showing otherwise, is a delivery technique that is the same as one or more of those indicated in the claim (e.g., intravenous, sublingual, or intramuscular). Different members of the classes of drugs (i.e., the peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) agonist and the ansamycins) are likely administered in a plurality of different ways depending upon their formulation and pharmacokinetic properties, but in each case the route is expected to have been determined suitable, safe, and effective.

Thus, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have determined the most appropriate doses, schedules, and routes of administration, so as to practice the disclosed process of treating the condition as effectively as possible. One ordinarily skilled in the art at the time the invention was made to do so to optimize the effectiveness of the treatment.

Absent a showing of any unobvious differences, it is therefore submitted that the process disclosed by the prior art would render obvious the process that is claimed.

This position is reasonable since parameters such as dosing, scheduling and routes of delivery, which are used to treat any given condition, may be expected to differ from those that are used most effectively to treat another condition. In general, these parameters that are used most efficaciously can only be determined in clinical trials designed to determine those parameters. The Office, however, does not have the facilities or resources for conducting clinical trials to determine if therapeutic agents are used effectively in particular regimens, as in accordance with the claims; so, in the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed process is different than that taught and/or suggested by the prior art. See In re

*Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977) and *Ex parte Gray*, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

Applicant has argued that the prior art does not teach that the NSAID described by the prior art modulates the PPAR-gamma pathway, but ciglitazone and rosiglitazone are in fact peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) agonists; and besides, the specification discloses: "One therapeutic treatment known to act on the PPAR $\gamma$  is the group of non-steroidal anti-inflammatory drugs, otherwise known as 'NSAIDS' " (paragraph [0006] of the published application). Thus, in accordance with this disclosure, the NSAID is a drug that "modulates the PPAR-gamma pathway" and apparently the property of an NSAID to do so is an inherent property of that class of drugs.

Applicant has also argued that neither ciglitazone nor rosiglitazone are NSAIDs. In response, since the specification does not define the NSAID as necessarily having any functional property other than the ability to act on PPAR $\gamma$ , which is significantly expressed in primary prostate cancer but at very low levels in normal prostate tissue, so as to make it a promising target for molecular therapy (paragraphs [0005] and [0006] of the published application), and since ciglitazone and rosiglitazone PPAR $\gamma$  agonists, at least for the purpose of construing the claims, it is submitted that both drugs are reasonably deemed the same as the "NSAID" to which the claims are directed. Notably, too, since Dorland's Illustrated Medical Dictionary<sup>13</sup> defines the term "NSAID" as meaning "any in a large group of drugs that are analgesic (pain-reducing), antipyretic (fever-reducing), and antiinflammatory (inflammation-reducing)" (Copyright © 2007 Elsevier; Copyright © 2002-2008 Merck & Co., Inc., Whitehouse Station, NJ, USA), though not as having any particular structure or mode of action, it is difficult to argue otherwise without first further limiting the material, structure, or function of the claimed "NSAID".

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<sup>13</sup> See Footnote # 5.

***New Grounds of Objection***

***Claim Objections***

20. Claim 29 is objected to as being directed in the alternative to the subject matter of a non-elected species of invention.

***New Grounds of Rejection***

***Claim Rejections - 35 USC § 112***

21. Claims 10-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10-19 are drawn to a method of treating a "cancer regulated by HER-kinase axis activation that is resistant to therapeutic treatments directed exclusively at either the PPAR-gamma pathway or the HE-kinase axis".

It is submitted that this recitation is not merely broad, but renders the claims indefinite for the following reasons:

It is reasonably presumed that Applicant does not regard every known "cancer" to be treatable using the claimed invention, but only certain types.

Yet, at paragraph [0001], for example, of the published application, the specification merely discloses that "[e]mbodiments of the present invention are directed to methods for treating and preventing disease conditions that are modulated by the PPAR $\gamma$  pathway and HER-kinase axis, such as cancer".

Dorland's Illustrated Medical Dictionary<sup>14</sup> defines the term "cancer" as meaning "any malignant, cellular tumor, referring to neoplastic diseases in which there is a transformation of normal body cells into malignant ones"; wherein the term "tumor" is defined as: "a new growth of tissue in which cell multiplication is uncontrolled and progressive"; and the term "malignant" is defined as: "having the properties of

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<sup>14</sup> Available on the Internet at:  
[http://www.mercksource.com/pp/us/cns/cns\\_hi\\_dorlands\\_split.jsp?pg=/ppdocs/us/common/dorlands/dorland/two/000016439.htm](http://www.mercksource.com/pp/us/cns/cns_hi_dorlands_split.jsp?pg=/ppdocs/us/common/dorlands/dorland/two/000016439.htm).

anaplasia, invasiveness, and metastasis" (Copyright © 2007 Elsevier; Copyright © 2002-2008 Merck & Co., Inc., Whitehouse Station, NJ, USA).

Notably cancer is not defined in such a manner that it is evident that it is necessarily a disease that is modulated by the PPAR $\gamma$  pathway and HER-kinase axis, nor is it evident that cancer should always be thought of as a disease that is "regulated by HER-kinase axis activation that is resistant to therapeutic treatments directed exclusively at either the PPAR-gamma pathway or the HER-kinase axis".

To the contrary, as before noted, cancer is a term that is used to describe any of a large number of diseases affecting a multitude of different cells and/or tissues; and such different types of cancer have markedly different etiologies and pathologies.

Which cancers are "regulated by HER-kinase axis activation"? How does one determine which types of cancer are "regulated by HER-kinase axis activation"?

What does "regulated by HER-kinase axis activation" mean?

Which treatments are "directed exclusively at either the PPAR-gamma pathway or the HER-kinase pathway in a mammal"?

How might one know or recognize a cancer that is resistant to such treatment if it cannot be ascertained which treatments are those that are "directed exclusively at either the PPAR-gamma pathway or the HER-kinase pathway"?

In this instance, since it is not known and cannot be determined how one knows or recognizes whether a cancer is regulated by the "HER-kinase axis" or how one distinguishes treatments that are directed exclusively at either the PPAR-gamma pathway or the HER-kinase pathway in a mammal, it cannot be ascertained whether cancer is regulated by HER-kinase axis activation or whether the cancer is resistant to such treatments.

As such, there is no means by which one can know or determine whether any given process infringes the claims, so as to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

22. Claims 10-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "new matter" rejection.

Claims 10-19 are drawn to a method of treating a "cancer regulated by HER-kinase axis activation that is resistant to therapeutic treatments directed exclusively at either the PPAR-gamma pathway or the HER-kinase axis".

Applicant has remarked that written support for the language of the claims is found in the specification, as originally filed, at, e.g., page 5, lines 19-21.

The disclosure to which Applicant has specifically referred reads as follows:

A significant limitation in therapeutic treatments directed exclusively at either the PPAR $\gamma$  pathway or the HER-kinase axis is that recipients thereof tend to develop a resistance to their therapeutic effects after they initially respond to therapy.

This disclosure to which Applicant has specifically referred as providing support does not describe the claimed invention, per se, and it does not even describe the use of the disclosed combination of drugs to treat only cancer that is resistant to initial therapy. Then, at paragraph [0001], for example, of the published application, the specification discloses that "[e]mbodiments of the present invention are directed to methods for treating and preventing disease conditions that are modulated by the PPAR $\gamma$  pathway and HER-kinase axis, such as cancer", but not necessarily of the claimed genus of cancer, which is "regulated by HER-kinase axis activation that is resistant to therapeutic treatments directed exclusively at either the PPAR-gamma pathway or the HER-kinase axis".

As such, it appears that there may be inadequate written support for the language of the present claims since the specification, as originally filed, fails to describe treatment of any of a plurality of different types of cancer that are "regulated by HER-kinase axis activation that is resistant to therapeutic treatments directed exclusively at either the PPAR-gamma pathway or the HER-kinase axis".

For these reasons it appears that the amendment to the claims has introduced new concepts, which were not before presented by the specification, as originally filed,

Art Unit: 1643

thereby violating the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

Perhaps this issue might be remedied if Applicant were to particularly point out other disclosures in the specification, as originally filed, which are believed to provide the necessary written support for the language of the instant claims.

### ***Conclusion***

23. No claim is allowed.

24. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1643

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/Stephen L. Rawlings/  
Primary Examiner, Art Unit 1643

slr  
August 30, 2009